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Review Article

STUDY OF DIFFERENT DRUG WHICH GIVE TERATOGENICITY EFFECTS IN PREGNANCY

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ABSTRACT

Teratogenicity refers to the capability of certain substances, including drugs, to cause congenital abnormalities or malformations in a developing fetus. This study explores the historical context, mechanisms, and various categories of teratogenic agents with a particular focus on pharmaceutical drugs. The investigation covers commonly prescribed medications such as ACE inhibitors, NSAIDs (like diclofenac), thalidomide, antineoplastic agents, antiepileptic drugs (e.g., valproic acid), anticoagulants (e.g., warfarin), and retinoids, examining their teratogenic mechanisms and effects. The study also discusses chemical agents (e.g., alcohol, cocaine, methyl mercury, lead), maternal factors like diabetes and epilepsy, and physical agents including cigarette smoke and ionizing radiation, all of which contribute to fetal anomalies. Notable congenital conditions such as spina bifida, hypocalvaria, fetal alcohol spectrum disorders (FASD), polydactyly, facial dysmorphia, and clubfoot are highlighted as outcomes of these exposures. Understanding the mechanisms of teratogenicity, critical exposure periods, and the importance of prevention strategies is crucial for minimizing risk during pregnancy. This study reinforces the need for healthcare professionals to critically assess the risk-benefit profile of medications prescribed during pregnancy.

Keywords: Teratogenicity, Congenital Malformations, ACE Inhibitors, Maternal Factors, Chemical Teratogens, Drug Safety, Birth Defects.

INTRODUCTION

The term Teratogens was first described in Paris, France in early 1932. Teratogens comes from the Greek word teras, which means monster or marvel (Karagiozova, 2017). Teratogens are environmental agents such as drugs, viruses, lack of nutrients, and physical or chemical elements that upon contact with embryo/fetus can cause congenital anomalies, generating permanent functional or morphological changes in the newborn (Thiago *et al*., 2017).

Congenital anomalies are the leading cause of infant mortality in high-income countries and the second most common cause in many middle-income countries. Such conditions emerge during fetal development and can be inherited or influenced by environmental factors, such as medication exposure (Gomes *et al*., 2021). Teratogenesis signifies the structural malformations during fetal development, in distinction from other kinds of drug induced fetal damage such as growth retardation, dysplasia (e.g. Iodine-deficiency-related goitre), or the asymmetrical limb reduction. The exposure of teratogenic chemical priorto conception, during prenatal or postnatal development leads to

manifestations of developmental toxicity including the death of the developing organism, structural abnormality, altered growth, and functional deficiency (Prasad *et al*., 2014). Exposure to trace amounts of nitrous oxide is not associated with impaired fertility or an increased risk of developing cancer; however, recent studies seem to suggest a correlation between nitrous oxide anesthesia and hyperhomocysteinemia, an independent risk factor for coronary artery disease. Long-term exposure to high concentrations of nitrous oxide may cause megaloblastic bone-marrow depression and neurological symptoms (Shayne, 2005).

Different types of the teratogens are-

Chemical substances, such as prescription medications like thalidomide and retinoic acid; illicit substances such as alcohol and cocaine; environmental toxins including heavy metals like cadmium; and pollutants like pesticides linked to reproductive and fertility problems, like diethylstilbestrol during pregnancy.

Infections including as rubella and Zika virus.

Physical constraint or in-utero damage, such as clubfoot from oligohydramnios, where the amniotic fluid is lost and the foetus is restricted, can occur. Amniotic band syndrome is one kind of physical harm that occurs to a fetus while it is still inside the mother. In severe situations, the condition can result in death.

History of Teratogenicity

Teratology is the science that studies the causes, mechanisms, and patterns of abnormal development. Teratology as a modern science was born in the 1930s with the publication of a set of experiments in which pregnant pigs were fed a diet deficient in vitamin A. All of these piglets suffered a variety of malformations, predominantly a lack of eyes.

The first human teratogen identified in 1941 by an ophthalmologist, Norman Gregg, was maternal rubella infection in pregnancy, which produced a triad of defects (cataracts, heart malformations, and deafness) in the infants (Sura and Christina, 2015). Nearly 60 years ago thalidomide was prescribed to treat morning sickness in pregnant women. What followed was the biggest man-made medical disaster ever, where over 10,000 children were born with a range of severe and debilitating malformations. Despite this, the drug is now used successfully to treat a range of adult conditions, including multiple myeloma and complications of leprosy.

How drugs affect the fetus

Drugs that a pregnant woman takes can affect the fetus in several ways. They can act directly on the fetus causing damage or abnormal development leading to birth defects or death. They can also alter the function of the placenta usually by constricting blood vessels and reducing the blood supply of oxygen and nutrients to the fetus from the mother and thus resulting in a baby that is underweight and underdeveloped. Moreover they can cause the muscles of the uterus to contract forcefully; indirectly injuring the fetus by reducing the blood supply or triggering pre-term labor and delivery

Teratogenic Factors

Teratogens are mainly classified into four types: Drugs, chemicals, maternal factors, physical factors (Porter, 2004).

Drugs

ACE inhibitors: (captopril and Enalapril)

Angiotensin-converting enzyme inhibitors (ACEIs) are the mainly indicated medications

in the treatment of cardiovascular and renal diseases, with heart failure, acute coronary syndrome, nephrotic syndrome, diabetes, and hypertension.

The ACE inhibitors are competitive inhibitors of kininase II, They affect both the Angiotensin/aldosterone and bradykinin/prostaglandin systems, Fetal wastage

Administration of ACE inhibitors during pregnancy leads to fetal wastage. Specifically, these drugs were associated with increase infant risks for cardiovascular and nervous system anomalies (Harlan, 2006). They cause severe renal and other problems during the second and third trimesters; these drugs should be avoided during pregnancy (Friedman, 2006).

Fetotoxic effects of ACE inhibitors consist of fetal hypotension, renal tubular dysplasia, anuria and oligohydramnios, growth restriction, hypocalvaria, and death when used in the second and third trimesters of pregnancy (Murki, 2005).

Non - steroidal anti-inflammatory agents: Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug and usually used by reproductive age women for the treatment of variety of conditions. Because of its low molecular weight diclofenac can readily crosses the human placenta during the first trimester.

Diclofenac can readily crosses the human placenta, Accumulates in fetal tissue, Induce skeletal and heart defects and fetal growth retardation

Pregnant women treated with high toxic doses of non-selective cyclooxygenase inhibitors show bone developmental variations in fetus. Drugs of this class like aspirin inhibit synthesis of vasodilator prostaglandin, causing temporary vasoconstriction and provoking malformations and cellular death (Chan *et al*., 2001). Administration of NSAIDs during the latter part of pregnancy may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, embarrassment of platelet aggregation, and delay labor and delivery.

Thalidomide

Thalidomide used as a sedative to treat morning sickness in pregnant women. Thalidomide is effective for lepra patients. Thalidomide can inhibit the production of tumour necrosis factor-α (TNF-α) in stimulated human monocytes. In addition, thalidomide and its derivatives can regulate the production of several cytokines, interleukin-2 and interferon γ. Thalidomide inhibit angiogenesis.

Thalidomide causes injure to the forming embryo in a short time susceptible window also known as the "critical period." The time susceptible window extends among days 20 and days 36 after fertilization (34–50 days after last menstrual cycle) (Vargesson, 2015). It has been established that thalidomide administration during the early stage of pregnancy significantly increases the incidence of miscarriage and the birth of malformed newborns with limb reduction anomalies and other defects, as well as congenital heart disease, ear and eye damage, and internal organ injure.

Androgen hormones: oestrogen

Androgens are a group of sex hormones. Natural androgens are steroidal hormones produced by gonands and adrenal glands. They help begin puberty and play a role in

reproductive fitness and body development. Testosterone is the generally common androgen (Maguoleun, 1983).

Increased level of androgenic hormones during pregnancy causes masculinisation of a female foetus. Masculinisation means to cause male characteristics in female and pseudohermaphroditism in pregnant mother. The androgenic progestin administered to the mother is changed to an oestrogen that does not protect the foetus from the masculinisation effect and causes cornification of the vagina. Testicular testosterone produced during a critical prenatal period is thought to masculinize and defeminise the male brain from the inherent feminization program. These actions of testosterone show to be exerted not through its androgenic activity, but rather throughout its conversion by brain aromatase into oestrogen, with the ensuing activation of oestrogen receptor mediated signaling (David, 2020).

Antineoplastic Agents

Antineoplastic drugs are medications used to treat cancer. Other names for antineoplastic drugs are anticancer, chemotherapy and cytotoxic drugs. The use of antineoplastic agents in pregnant women poses noticeable risks to both the patient and the developing fetus, particularly during organogenesis. Congenital malformations can occur in just about 20% of cases if chemotherapy using cytotoxic anticancer drugs is administered through the first trimester (Blagosklonny, 2005).

If the patient is pregnant while receiving chemotherapy, termination of pregnancy is an option as there is an enlarged risk of drug-induced fetal malformations. Patients with breast cancer sensitive to premenopausal hormones may miss their chance to become pregnant, as the postoperative administration of tamoxifen may be extended term (Shingo *et al*., 2016).

Methotrexate

It is a synthetic analogue of dihydrofolate and acts as competitive inhibitors of dihydro folate reductase (DHFR) enzyme. Methotrexate causes trouble in folate metabolism and may have a teratogenic effect through inhibition of the folate methylation cycle. Birth defects in children born to women who have been treated with methotrexate contain skeletal defects, low birth weight, and a wide range of developmental abnormalities

Anticoagulant Agents: Warfarin

Warfarin is the competitive inhibitor of vitamin K. Warfarin can easily cross the placental barrier and enters the fetal bloodstream. It has a lower molecular weight, causing fetal warfarin syndrome-children. Warfarin crosses the placenta and is related with increased rates of fetal loss. Warfarin taken throughout the second and third trimester causes central nervous system anomalies (Nene *et al*., 2011). Consuming higher doses of warfarin greater than 5mg daily can immediately result in fetal death. Warfarin syndrome can be prevented by not prescribing the warfarin drug to the women trying to suppose and avoid it before five days of conception.

Valproic Acid

Valproic acid (VPA) is a commonly prescribed drug for those affected by epilepsy and bipolar disorders. VPA has a well known teratogenic prospective, causing a variety of birth defects with neural tube defects (NTDs) and other congenital malformations, when women are treated with this medication

during pregnancy (Fath *et al*., 2014). Valproic acid causes valproate syndrome. It increases in the rate of developmental problems, manifested by decreased verbal intelligence often with communication problems of the autistic spectrum disorder (ASD) (Asher Ornoy, 2009).

Retinoic Acid

Retinoids are vitamin A i.e retinol derivatives. Vitamin A (retinol) is an essential vitamin that helps to regulate cellular differentiation of epithelial tissue (Tantibanchahai, 2014). Excess of vitamin A can concern embryonic development and result in teratogenesis in a developing embryo. The concerned organs are the fetal skull, face, limbs, eyes, central nervous system due to excess retinoids. Avoiding the retinoids excess during pregnancy can make the baby sleep in this world as an entire human with no defects (Marill *et al*., 2003).

Chemical Factors

Unnecessary chemical

Alcohol

During the primary four weeks of pregnancy, the baby develops organ systems in their body, such as the heart, central nervous system, eyes, arms, and legs. The baby's brain starts developing about the third week of its intrauterine life and gradually matures together with the pregnancy.

Alcohol exposure during pregnancy can have direct toxic and teratogenic effects on a fetus, Ethanol diffuses through the placenta and distributes quickly into the fetal compartment, accumulating in the amniotic fluid.

MOA:

The mother consumes alcohol

- It can easily bypass through the placenta
- Interfere with growth factor that regulate cell division in cerebral cortex of foetus
- Preventing the normal growth and fetal brain development
- Developmental exposure can result in fetal alcohol spectrum disorders (FASDs)

The maternal and fetal endocrine systems are also reported to be affected by alcohol in a number of ways, and the maternal-fetal endocrine balance may also be disrupted (Colleen, 2002). Alcohol is a known as toxicant it causes cell death in a fetus, and a teratogen, altering cell cycle and function in a developing fetal brain, with PAE having instant and persisting effects on an individual among FASDs (Dae *et al*., 2021).

Prevention: One can barrier these changes by avoiding alcohol expenditure during pregnancy and protecting the baby from fetal alcohol spectrum disorder.

Cocaine

Cocaine is an alkaloid and nitrogen-based natural compound. It is a drug with probable local anaesthetic effect and properties like painkiller and antidepressant.

Cocaine works as a central nervous system stimulant by interfering with the nervous cells reuptake of nor epinephrine and dopamine. Nor-epinephrine and dopamine are chemicals involved in the transmission of neurological signals, or neurotransmitters. Slowed reuptake causes raise in levels of neurotransmitters like Dopamine (Tantibanchahai and Zhang, 2013). Increased levels of nor-epinephrine enable cocaine to accumulate at nerve terminals, which in pregnant women results vasoconstriction and hypertension at the site where the uterus and placenta attach together.

This disturbance of blood flow to the uterus and placenta may also result in maternal tachycardia, a condition that manifests in an abnormally high heart rate, an amplified risk for ventricular arrhythmias, and amnion rupture, which in turn causes limb defects in the fetus .The effective vasoconstrictive effects of cocaine when exposed during the first trimester may increase the risk of structural abnormalities.

Other Chemicals

Methylmercury

Methylmercury is generally known for its variable toxicity such as neurotoxin, endocrine disruptor and teratogen. Exposure of methylmercury produces changes in behaviour and health in humans. Prenatal exposures of methylmercury in humans at high concentration outcome in neurobehavioral effects such as cerebral palsy and severe mental retardation. It is also associated with decreased birth weight and early sensor motor dysfunction such as late onset of walking.. It also produces developmental neurotoxic effects in fetus and infant. To avoid these teratogenic effects, pregnant women and women of childbearing age are possible to avoid exposure of methylmercury.

Lead acetate

Lead is common industrial and public health problem that causes numerous adverse effects in both men and women. A woman who has lead poisoning can pass lead to her fetus if she becomes pregnant. The term “lead poisoning” refers to blood Pb levels ≥50 µg/dl. Harmful effects of lead exposure have not been credibly shown to occur at blood Pb levels ≤20 µg/dl. Lead crosses the placenta as early as the 12th to 14th weeks of gestation and accumulates in fetal tissue (Wang *et al*., 2009). The adverse effects of lead consist of spontaneous abortion and stillbirth. A small but most important increase in minor malformations, including haemangioma, lymph-angiomas, skin tags, skin papillae, and was seen in infants with elevated lead levels in the umbilical blood. The VACTERL (vertebral, anal, cardiac, tracheoesophageal fistula, renal and limb abnormalities) organization has been reported with prenatal exposure to high lead levels (Enid, 2010). Serious effects of lead exposure include increased prevalence of menstrual disturbances, spontaneous abortion and threatened abortion.

Maternal Factors

Diabetes Mellitus

Diabetes mellitus is an assembly of physiological dysfunctions categorized by hyperglycaemia resulting directly from insulin resistance, insufficient insulin secretion, or extreme glucagon secretion. Insulin is a hormone in the body of human. Insulin helps to obtain enough glucose into the body cells to be used as fuel whenever there is no exterior food source.

Types of Diabetes Mellitus are:

- Type 1 diabetes (T1D)
- Type 2 diabetes (T2D)
- Type 3 gestational diabetes

Gestational diabetes in which blood glucose levels rise and various diabetic symptoms rapidly appear through pregnancy, as the same women may not be diagnosed as diabetic before. This is general for pregnant women.

Diabetes is responsible for a defeat of normal homeostasis not only of carbohydrate but of fat and protein metabolism as well (James, 2010). The placenta is an organ that provides

the baby with all the nutrients and oxygen essential to grow, lactogen, and cortisol. All the mentioned hormones can block the insulin. This blockade is known as insulin resistance. It is insulin resistance that results in excess amounts of insulin in the mother's body and can produce surplus sugar levels in the blood giving rise to gestational diabetes. women has type II diabetes, has difficulties with multiples or with twins, lack of physical activity, polycystic ovarian syndrome, before given birth to a baby of weight greater than nine pounds. Difficulties for the infant of a diabetic mother are stillbirth, birth anomalies mainly in the first trimester of pregnancy, macrosomia, birth injury, hypoglycemia, respiratory distress and preeclampsia.

Precautions: Even though a woman had gestational diabetes before, the risk can also be lowered for the next pregnancy if they follow a healthy way of living and eating foods advanced in fibre content, low fat, and calories. Devouring fruits, vegetables, and whole grains, along with watching the portion sizes, is suggested. Exercising daily for 30 min of a moderate workout can help you plan for your pregnancy at a healthy weight, not more than the recommended weight during pregnancy. All the above mentioned factors will help to defeat gestational diabetes.

Epilepsy

Epilepsy is a disorder in which nerve cell activity in the brain is anxious, causing seizures. Epilepsy may occur as a result of a genetic disorder or an acquired brain damage, such as a trauma or stroke. Epilepsy and pregnancy interrelate in a complicated way. Antiepileptic drugs (AEDs) have usual chronic teratogenic effects, the most common of which are congenital heart disease, cleft lip/palate, urogenital defects, and neural tube defects (Betul *et al*., 2017). Phenytoin is most commonly used antiepileptic medications. If phenytoin is administered by the mother in the first trimester, there is approximately a 5 to 10 percent chance that the baby could be born with a combination of birth defects known as the Fetal Hydantoin Syndrome that includes abnormalities like short nose, low or broad nasal bridge, epicanthic folds, hypertelorism, microcephaly, abnormal ears, wide mouth, oral clefts, hypoplasia of distal phalanges, short/webbed neck, low hairline, irregular mental development and abnormal motor development.

Valproic acid (VPA) is a usually prescribed drug for those affected by epilepsy and bipolar disorders. VPA has a well known teratogenic potential, causing a range of birth defects including neural tube defects (NTDs) and other congenital malformations, when women are treated with this medication during pregnancy.

Precautions: In spite of these risks, seizure control through pregnancy is very important. Therefore, when a woman with epilepsy is planning a pregnancy, it is important for her to meet with both her neurologist and her obstetrician, before conception, to discuss the definite treatment to be used to manage seizures while pregnant.

Physical agents

Cigarette

Smoking Cigarette smoking by the mother is one of main reasons of general developmental abnormalities. Reduced development in fetus is observed. The range of chemicals like nicotine, carbon monoxide and cyanide released during tobacco smoking obstruct

with the transport of amino acids across the placenta. Carbon monoxide formed during smoking crosses placenta and increases carboxyhemoglobin levels in blood which has longer half-life in fetal blood than in maternal blood. Nicotine released during cigarette smoking has vasoconstriction effect that grades in uterine vascular constriction and intrauterine growth retardation because of decreased perfusion of fetal tissues. It also increases the risk of prenatal death. The prenatal mortality that is death recognized to abruption placenta, placentaprevia, impulsive abortion, prematurity and intrauterine growth retardation, preterm delivery, prenatal mortality, sub fertility, unusual placentation, childhood morbidity and mortality, congenital malformations, gastroschisis, cardiac defects, chromosomal abnormalities and central nervous system problems.

Ionizing radiation

The cell loss or chromosome injury is the ordinary reasons of embryo injury by ionizing radiation. Exposure of radiations 8-15 weeks after fertilization is the mainly critical exposure period vital to toxicity. The exposure leads to numerous effects such as human embryos abortion, malformations, and intrauterine growth retardation and has early- or late-stage onset genetic disease of which permanent growth retardations additional severe. The CNS is mainly affected by radiation exposure and leads to CNS abnormalities like early microcephaly, mental retardation and later increases incidence of hematopoietic malignancies and leukaemia. Excessive exposure to radiation causes chromosomal fragmentation, and alters DNA structure main to mutations.

Teratogenic defects in infants

Spina Bifida

Spina bifida is a birth defect in which a developing baby's spinal cord fails to develop appropriately. It's a form of neural tube defect. Spina bifida is a congenital malformation in which the spinal column is split as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization. In its commonest and most severe form, myelomeningocele (MMC) the spinal cord is open dorsally, forming a placode on the back of the fetus or newborn baby that normally rests on a meningeal sac. Individuals with MMC often reveal motor and sensory neurological shortage. This may result in lower limb weakness or paralysis that prevents walking, and lack of sensation. Urinary and fecal incontinence occur commonly.

Mechanisms and pathophysiology

The primary disorder in the pathogenesis of MMC is failed neural tube closure in the embryonic spinal region, which leads to prolonged exposure of the open neural tube to the amniotic fluid environment. The bifid neuroepithelium initially undergoes relatively normal neuronal differentiation, with development of spinal motor and sensory function even below the lesion level. As gestation progresses, however, the uncovered spinal cord becomes haemorrhagic and neurons expire as a effect of toxicity of the amniotic fluid. Axonal connections are interrupted, and function is lost Hence, neurological disability in MMC is often measured a ‘two-hit’ process: failed neural tube closure followed by neurodegeneration in utero (Andrew, 2015).

Treatment: Spina bifida treatment depends on the rigorousness of the condition. The two major Spina bifida treatment options are fetal surgery in the duration of pregnancy or surgery on the baby after birth. Prenatal surgery for Spina bifida takes place previous to the 26th week of pregnancy.

Hypocalvaria

The calvaria are the top part of the skull. It is the superior part of the neurocranium and covers the cranial cavity containing the brain. It forms the main component of the skull roof. The calvaria are made up of the superior portions of the frontal bone, occipital bone, and parietal bones. Hypocalvaria is a condition in which the skull is absent. It happens often after using ACE Inhibitors while pregnancy. Hypocalvaria is its hypoplastic alternative where the skull bones are moderately produced. Due to such a exceptional incidence, it has been given the status of an orphan disease. The cause of the hypoplastic calvaria found with ACE inhibitor exposure is unknown. Endochondral bone and membrane bone grow and develop in entirely different ways. Long bones require low oxygen tension because nutrition takes place by diffusion through the cartilaginous epiphyses. Membrane bones, on the other hand, have the high degree of vascularity necessary for their own growth, and high oxygen tension is required. The presumed hypotension produced by ACE inhibitor exposure may result in hypoxic effects and thus hypoplastic calvaria (Barr and Cohen, 1991).

Precautions: a lesser amount of exposure or avoidance of ACE inhibitor can avoid hypocalvaria.

Fetal Alcohol spectrum disorders Fetal alcohol spectrum disorders (FASDs) are a set of conditions that can occur in a person whose mother drank alcohol in the duration of pregnancy. FASDs can arise when a person is exposed to alcohol prior to birth. Alcohol in the mother's blood passes to the baby throughout the umbilical cord. Symptoms includes an irregular appearance, short height, low body weight, little head size, poor coordination, behavioural difficulty, learning problems, and problems with hearing and view. The risk of FASD depends on the quantity consumed, the frequency of consumption, and the points in pregnancy at which the alcohol is consumed.

Precautions: To prevent FASDs, a woman should evade alcohol if she is pregnant or might be pregnant. FASDs are escapable if a baby is not exposed to alcohol before birth.

Facial dysmorphia

Dysmorphic feature is a congenital disorder, genetic syndrome, or birth defect. It is isolated dysmorphic syndrome. Dysmorphic features may contain craniofacial dysmorphism, skeletal abnormalities and short proximal limbs and renal cysts in different disorders linked to peroxisomal dysfunction

1. Dysmorphic features may effect from a perturbation of human development Dysmorphic facial features with arched eyebrows, broad nasal root, low set ears, downward sloping eyes, epicanthal folds, strabismus, and myopathic face were noticed (Jones and Adam, 2015).

Treatment: Treatment for body dysmorphic disorder includes a combination of cognitive behavioural therapy and medications. Medications includes selective serotonin

reuptake inhibitors (SSRIs) like Lexapro, Prozac, fluvoxamine

Polydactyly

Polydactyly is a condition in which a baby is born along with one or more extra fingers. It is a common condition that frequently runs in families. The extra fingers are generally small and abnormally developed. As a baby develops in their mother's womb, the hand first forms in the shape of a paddle and later divides into split fingers. If this process continues a bit longer than normal, a single finger divides again, creating an extra finger.

Treatment: Polydactyly is usually treated in early childhood with the removal of the extra finger or toe. If the extra digit is not attached with bones, a vascular clip may be used to remove it. The vascular clip attaches to the extra finger and cuts off blood flow to it. This usually occurs when a child is between 1 and 2 years old. At this age, children are young enough not to miss developmental milestones, such as grasping for objects, but old enough to better tolerate anaesthesia and surgery.

Clubfoot

Clubfoot describes an array of foot abnormalities generally present at birth (congenital) in which baby's foot is twisted out of shape or position. In clubfoot, the tissues connecting the muscles to the bone and tendons are shorter than normal. Clubfoot is a quite common birth defect and is generally an isolated problem for an otherwise healthy newborn. Clubfoot may be mild or severe. About half of children with clubfoot having in both feet. The cause of clubfoot is may be a combination of genetics and environmental agents. Boys are about twice as likely to develop clubfoot as girls. Risk factors includes Family history, congenital conditions, Environment, Not sufficient amniotic fluid during pregnancy, Smoking during pregnancy can extensively increase the baby's threat of clubfoot.

Treatment: Because newborn's bones, joints and tendons are very flexible, treatment for clubfoot usually begins in the first week or two after birth. The goal of treatment is to improve the way child's foot looks and works before he or she learns to walk.

Treatment options includes

- Stretching and casting
- Surgery

Prevention: The clubfoot can be prevented by avoiding smoking, alcohol and drugs not approved by doctor.

Conclusion

Table 1: Historical events in modern teratology

Year	Historical event
1905	The first experimentally induced developmental toxicity in mammals. Embryonic lethality induced by X-rays in cats (Tousey)
1921	The first experimentally induced teratogenicity in mammals. Disorders in limbs in pigs induced by lipid diet
1929	The first description of malformations in humans caused by exogenous factors. Microcephalia caused by X-ray irradiation of the pelvis (Goldstein and Murphy).
1935	Recognition of food deficiency leading to malformations in animals. Eye disorders in pigs due to hypovitaminosis A (Hale).

1937	Hormones causing alterations in sexual differentiation in animals. Masculinisation of female foetuses in mice due to theaction of androgens (Raynaud)
1941	Report on virus-induced human malformations. Rose-rash induced eye disorders (Gregg).
1944	The first evidence of postnatal effect following prenatal administration of a chemical substance. Decreased learning ability inrats caused by the administration of sodium bromide (Hamiltonand Harned).
1948	General recognition of chemically induced teratogenicity. Experiments with alkylating agents (Haskin) and trypan blue
1952	The first report on malformations caused by drugs in humans.Multiple malformations in foetuses caused by aminopterin(Thiersch).
1959	The first report on human malformations induced by environmental pollutants. Disorders of the central nervous system anddentition caused by methyl mercury
1961	Thalidomide-induced embryopathy

Table 2: Factor of Teratogenicity

Sr. No	Factors	Medication
A	Drugs	ACE Inhibitors (captopril, enalapril) NSAID (Diclofenac), Thalidomide, Androgen hormone (oestrogen), Antineoplastic agents (methotrexate), Warfarin, Valproic acid, Retinoic acid
B	Chemicals	Alcohol, Cocaine, Methyl mercury, Lead Acetate.
C	Maternal Factors	Diabetes Mellitus, Epilepsy
D	Physical Agents	Cigarette Smoking, Ionizing radiation.

Table 3: Teratogenic Drugs in Pregnancy

Sr. No	Drug	Uses	References
Teratogenic Drugs in First Trimester of Pregnancy			
1	Valproic Acid	Fetal Hydantion Syndrome	Gilbert, 2010
2	Carbamazepine	treatment of epilepsy and bipolar disorder during pregnancy	Nie *et al*., 2016
3	Warfarin	several ophthalmologic and genetic problems	Cone-Wesson, 2005
4	Antidepressant	neurobehavioral problem	Gilbert, 2010 & Greenberg *et al*., 2011
5	Antithyroid	treat hyperthyroidism in pregnant patients	Gilbert, 2010
6	Retinoic Acid	cellular differentiation and tissue specificity	Gilbert, 2010
7	Benzodiazepine	treat hypertension or eclampsia and reduce anxiety in addition to issues with insomnia.	Gilbert, 2010
8	Streptomycin	For congenital deafness	Gilbert, 2010

9	Kanamycin	For congenital deafness	Gilbert, 2010
10	Topiramate	used for epilepsy and migraines	Hunt *et al*., 2008 & Huybrechts *et al*., 2018
11	Lamotrigin	safest mood stabilizer during pregnancy	Cunnington *et al*., 2005 & Tennis *et al*., 2002
Teratogenic Drugs in Second Trimester of Pregnancy			
1	Angiotensin Converting Enzyme Inhibitors	lowers the blood pressure by relaxing the veins and arterie	Gilbert, 2010
2	Diazepam	reduce anxiety and treat eclampsia in the second trimester of pregnancy	Gilbert, 2010
Teratogenic Drugs in Third Trimester of Pregnancy			
1	Tetracycline	used to manage and treat different bacterial infections These are assigned to patients falling in pregnancy category D (Evidence of risk pertaining to a risk to the fetus) by the FDA	Ross *et al*., 2000
2	Chloramphenicol	Form of ear drops to treat ear infections.	Denton *et al*., 2011
3	Aspirin	it reduces platelet aggregation	Denton *et al*., 2011
4	Indomethacin	delay delivery by at least 48 hours and as much as 7–10 days	Gilbert, 2010

CONCLUSION

Teratogenic drugs can cause serious birth defects if taken during pregnancy, especially in the first trimester. Medications like ACE inhibitors, thalidomide, and valproic acid, as well as substances like alcohol and lead, can harm fetal development and lead to conditions such as spina bifida, facial deformities, and growth retardation. Most of these effects are preventable through proper medical guidance, avoiding harmful substances, and raising awareness among women of reproductive age. Careful drug use and prenatal care are essential for healthy pregnancy outcomes.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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